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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/016,403	Applicant(s) HOLLADAY, LESLIE A.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-18* is/are pending in the application.

4a) Of the above claim(s) *5-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

[1] Claims 1, 2, and 4-18 are pending in the application.

[2] Applicants' election with traverse of Group I, claims 1, 2, 4, 17, and 18 in Paper No. 9, filed 12/09/02, is acknowledged.

Election/Restrictions

[3] Applicants traverse the restriction requirement by arguing that the inventions of Groups I-III are not independent or distinct inventions, but are different embodiments of the same invention as the inventions are intimately related to each other. Applicants argue the inventions of Groups I-III form the working basis for the claimed invention and separately the inventions do not have the necessary core of the invention in which to relate. Applicants further argue that the claims of inventions of Groups I-III are related and could be co-examined without a serious burden on the examiner. Applicants argue that because the claims are related to one another and, in the interest of efficiency, they should be co-examined in a single application. Applicants argue a complete search of the prior art would necessarily require a search of all the subject matter of Groups I-III. Applicants' arguments are not found persuasive.

Addressing applicants' argument that the inventions are not independent or distinct, the inventions of Groups I-III *are* independent or distinct for the reasons provided in items 2-4 of Paper No. 5. The inventions clearly are not embodiments of the same invention as Groups I and II are methods, while Group III is a product. Furthermore, the methods of Groups I and II are independent as they comprise different steps, utilize different products, and yield different results. Therefore, the inventions of Groups I-III are independent and distinct.

Addressing applicants' argument that all claims should be co-examined, a serious burden would be required for the examiner to search all claims of the instant application. A search for each of Groups I-III would require independent considerations that would require the examiner to focus on different features and entail differently structured text searches for both patent and non-patent literature for each

of the three claim groupings. For example, the claim of Group II would require a search for a pH range that is not recited in any of the claims of Groups I and III. Also, claim 10 of Group III would require a search for a physiological carrier of a peptide analog, a limitation that is not recited in either of Groups I and II. Thus, a search for all co-pending claims would require a separate search.

MPEP § 803 sets forth two criteria for restricting between patentably distinct inventions – 1) the inventions must be independent or distinct and 2) there must be a serious burden on the examiner. MPEP § 803 states, "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02". The inventions are independent or distinct and require a separate search for the reasons provided above and the reasons provided in items 2-6 of Paper No. 5. Thus, the two criteria for restriction have been satisfied and restriction for examination purposes is proper under 35 USC § 121.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that claim 16 was not grouped into any of Groups I-III in Paper No. 5. Claim 16 is drawn to a composition comprising a pharmaceutical polypeptide agent and would have been grouped with the claims of Group III.

Claims 5-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

[4] Receipt of an Information Disclosure Statement (IDS) in Paper No. 3, filed 02/28/02, is acknowledged.

[5] It is noted that the Sambrook et al., Hatch et al., and Seetharam et al. references have not been considered as these references merely consist of a title page and citation information, which does not comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.

Specification/Informalities

[6] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of Enhancing Electrotransport Polypeptide Flux by Amino Acid Substitution with Histidine". See MPEP § 606.01.

Claim Objection(s)

[7] Claim 18 appears to be grammatically incorrect. It is suggested that the term "the formulation used for delivering the analog by electrotransport having" should be replaced with, for example, "wherein the formulation used for delivering the analog by electrotransport has". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[8] Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in the recitation of "the same biological activity as the parent polypeptide agent". It is unclear from the claims and the specification as to whether this term is meant to be interpreted as meaning the analog has the same *type* of biological activity as the parent polypeptide, e.g., the analog retains the same enzymatic activity as the parent polypeptide, or the analog maintains the same *level or amount* of biological activity as the parent polypeptide, e.g., the analog maintains the same enzymatic rate as the parent polypeptide. For purposes of examination, the claim has been interpreted as meaning the analog maintains the same level of biological activity as the parent polypeptide. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[9] Claims 1, 2, 4, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for delivering by electrotransport a genus of pharmaceutical polypeptide agents having at least one amino acid residue replaced by His and optionally wherein the amino acid residue is Gln, Thr, or Asn, or wherein the analog exhibits the same biological activity as the parent polypeptide.

Regarding claims 1, 2, 17, and 18, it is noted that the specification defines a pharmaceutical polypeptide agent as "refer[ing] to any polypeptide... ...that has physiologic activity, i.e., bioactivity" (see page 8, lines 6-8 of the instant specification). Furthermore, the term "pharmaceutical" implies a utility for the treatment of a disease or condition, which typically requires a peptide or polypeptide having bioactivity. Thus, it appears from the definition provided in the specification that the pharmaceutical polypeptide agent as delivered by the claimed method is intended to exhibit biological activity upon delivery, and the examiner has interpreted the claims accordingly.

The specification teaches the structure of only a single representative species of such pharmaceutical polypeptide agents, i.e., human parathyroid hormone with glutamine at position 29 replaced with histidine (see page 18, Example 2). While the specification describes the structures of other polypeptides having amino acids substituted with His (see page 17, Example 1 and pages 18 and 19, Example 3), there is no disclosure or indication in the specification that these polypeptides maintain

biological activity. Moreover, the specification fails to describe any other representative species of pharmaceutical polypeptide agents that maintain biological activity upon amino acid substitution with His by any identifying characteristics or properties other than being a pharmaceutical polypeptide agent having one or more amino acids substituted with His. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. If applicants should traverse the rejection on the basis that the structures of polypeptides are not required in method claims or that method claims have a relaxed standard of written description, it is noted that the structures of the pharmaceutical polypeptide agents are an essential feature of the invention and therefore, require adequate written description under 35 USC 112, first paragraph.

[10] Claims 1, 2, 4, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivering human parathyroid hormone with glutamine at position 29 replaced with histidine by electrotransport, does not reasonably provide enablement for a method for delivering by electrotransport *any* pharmaceutical polypeptide agent having *any* residue or optionally, Gln, Thr, or Asn residue(s), replaced by His, and optionally wherein the analog exhibits the same biological activity as the parent polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to make and use the entire scope of claimed methods. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s). The Factors most relevant to the instant rejection are addressed below.

- Breadth of the claims: the claims are so broad as to encompass a method for delivering *any* pharmaceutical polypeptide agent having *any* Gln, Thr, or Asn residue(s) replaced by His by electrotransport, and optionally wherein the analog exhibits the same biological activity as the parent polypeptide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of pharmaceutical polypeptide agent analogs with any Gln, Thr, or Asn residue(s) replaced with His that optionally maintain equivalent activity relative to the parent polypeptide as broadly encompassed by the claims. In this case the disclosure is limited to a method for delivering human parathyroid hormone with glutamine at position 29 replaced with histidine by electrotransport. Regarding claims 1, 2, 17, and 18, as stated above, it is noted that the specification defines a pharmaceutical polypeptide agent as "refer[ing] to any polypeptide... ...that has physiologic activity, i.e., bioactivity" (see page 8, lines 6-8 of the instant specification). Furthermore, the term "pharmaceutical" implies a utility for the treatment of a disease or condition, which typically requires a peptide or polypeptide having bioactivity. Thus, it appears from the definition provided in the specification that the pharmaceutical polypeptide agent as delivered by the claimed method is intended to exhibit biological activity upon delivery, and the examiner has interpreted the claims accordingly.
- Lack of guidance and working examples: the specification has failed to provide the necessary guidance for making and using the entire scope of delivery methods as encompassed by the claims. The specification provides only three working examples to demonstrate the enablement of the claimed method. The working examples provide three polypeptides with mutation of Gln with His. There is disclosed only a single working example to demonstrate a peptide that retains biological activity upon mutation of Gln with His, i.e., human parathyroid hormone with glutamine at position 29 replaced with histidine (see example 2 at page 18 of the specification). No further guidance is provided for additional substitution(s) of Gln, Thr, or Asn with His with an expectation of a polypeptide maintaining at least partial biological activity or in the case of claim 4, activity equivalent to the parent polypeptide. Furthermore, if the bioactivity of the pharmaceutical polypeptide is reduced by mutation, the specification

provides no guidance regarding the level of bioactivity required for the mutant polypeptide to retain its pharmaceutical activity.

- The relative skill of those in the art and the unpredictability of the art: a skilled artisan would recognize that there is no method for accurately and reproducibly predicting the effects of a protein's activity following amino acid mutation. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. While techniques for altering a protein's amino acid sequence are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired bioactivity are limited in any protein and the result of such modifications is highly unpredictable. One of skill in the art recognizes that amino acid substitutions can result in an altered level or disruption of biological activity or a complete conversion from a first biological activity to a second, distinct biological activity. For example, Nishimura et al. (*J Biol Chem* 268:24041-24046) teach an Asn to His mutation at position 92 of Factor IX results in a significant decrease in binding affinity and causes a 1000-fold decrease in catalytic rate (see page 24046, left column, top). Also, Steadman et al. (*Biochemstry* 37:7089-7095) teach a Gln to His mutation at position 214 of human thymidylate synthase results in a 30 % decrease in catalytic rate and a 10-fold decrease in affinity for substrate (see page 7092, Table 2). In addition, one skilled in the art would expect any tolerance to a single amino acid substitution with His to diminish with each further and additional modification, e.g. multiple substitutions.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166

USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[11] Claims 1, 2, 4, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chien et al. (US Patent 5,250,022) in view of Green et al. (*Pharm Res* 8:1121-1127) and Markussen et al. (*Protein Engineering* 2:157-166). Claim 1 is drawn to a method for delivering a pharmaceutical polypeptide agent through a body surface by: (a) providing a synthetic analog of a pharmaceutical parent polypeptide agent having at least one amino acid substituted with His and (b) delivering the analog through the body surface by electrotransport. Claim 2 limits the amino acid of the parent polypeptide substituted with His of the method of claim 1 to Gln, Thr, or Asn. Claim 4 limits analog of the method of claim 1 to having the same level of biological activity as the parent polypeptide agent. Claim 17 limits the method of claim 1 to providing the analog in the form of an anionic donor reservoir formulation having a pH in the range of about 3.5 to about 7.4. Claim 18 limits the formulation of the method of claim 17 to having a pH in the range of 5 to 7.4.

Chien et al. teach methods for the administration of insulin as an ionizable pharmaceutical by iontophoresis (see especially column 11, line 56 through column 13, line 59). They further teach the use of pH's "at least about 1.0, 1.5 or about 2 pH units above or below the pKa or isoelectric pH of the ionized pharmaceutical" (column 3, lines 45-47); the isoelectric pH of insulin as 5.3 (column 6, lines 43-49); and the use of pH 3.6 buffer for their experiments (column 11-12, Example 1). They also teach that

peptide compounds related to various possible pharmaceuticals can be produced by using DNA recombinant techniques (see column 4, lines 16-30). They do not teach the use of insulin analogues or polypeptides substituted with histidine.

Green et al. teach the transdermal iontophoresis of tripeptides containing neutral, zwitterionic, anionic, or cationic amino acids. They further teach that anodal iontophoresis of a peptide containing the cationic amino acid histidine was enhanced at pH's where histidine is positively charged (see page 1124, left column and page 1126, right column) and that the enhancement was larger that that for any other peptide (compare Figure 5(a) to Figures 1, 3, 6, and 7).

Markussen et al. teach that biological potency was retained in insulin containing an asparagine to histidine substitution at position A21 (page 157, abstract).

At the time of the invention, it would have been obvious to one of ordinary skill in the art practicing the iontophoresis administration of insulin, as taught by Chien et al., to substitute a histidine-containing insulin polypeptide, as taught by Green et al. and Markussen et al., with the expectation of improving transdermal insulin delivery. Motivation to utilize an insulin polypeptide comprising an introduced histidine residue is provided by Green et al., who teach that the positive charge available at lower pH's results in enhanced iontophoresis transfer. One would have a reasonable expectation of success for enhanced iontophoresis transfer using insulin with Asn replaced with His at position A21 because of the results of Green et al. Therefore, claims 1, 2, 4, 17, and 18, drawn to a method for delivering a pharmaceutical polypeptide agent through a body surface by electrotransport would have been obvious to one of ordinary skill in the art.

Conclusion

[12] All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for official papers filed to Group 1600 is (703) 308-4242. Draft or informal FAX

communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit 1652

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